Docket No.: 04654/0200039-US0
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Gopalan Balasubramanian et al.

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: Concurrently Herewith

Art Unit: N/A

For: NOVEL TRICYCLIC COMPOUNDS USEFUL FOR THE TREATMENT OF INFLAMMATORY AND ALLERGIC DISORDERS: PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Examiner: Not Yet Assigned

AFFIRMATION OF PRIORITY CLAIM

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant hereby claims priority under 35 U.S.C. 119 based on the following prior foreign application filed in the following foreign country on the date indicated:

Country	Application No.	Date
India	922/MUM/2002	October 23, 2002

A certified copy of the referenced Indian Patent Application was received by the International Bureau on January 8, 2004 during the pendency of International Application No. PCT/IB2003/004442. A copy of Form PCT/IB/304 is enclosed.

Dated: April 20, 2005

Respectfully submitted,

By Ryan Barrison (53,970)

Jay P. Lessler
Registration No.: 41,151
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

04366/2200039-WO PCT/IB2003/004442

TO: Marie GILFILLAN

ATTY REVIEWED _____

DATE _____

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

SULLIVAN, Robert, C.
Darby & Darby P.C.
P.O. Box 5257
New York, NY 10150-5257
United States of America

Date of mailing (day/month/year) 09 January 2004 (09.01.2004)	
Applicant's or agent's file reference 2200039-WO0	**IMPORTANT NOTIFICATION**
International application No. PCT/IB2003/004442	International filing date (day/month/year) 08 October 2003 (08.10.2003)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 23 October 2002 (23.10.2002)
Applicant GLENMARK PHARMACEUTICALS LTD. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. (If applicable) The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. (If applicable) An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a **priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
23 Octo 2002 (23.10.2002)	922/MUM/2002	IN	08 Janu 2004 (08.01.2004)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

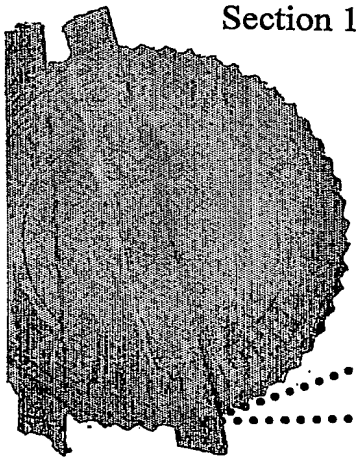
Authorized officer

Pascale CHOUQUER

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and provisional specification filed on 23.10.2002 in respect of Patent Application No. 922//MUM/2002 of Glenmark Pharmaceuticals Limited, an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No. 26511, Mumbai – 400 026, India.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.



Dated this 3rd day of October 2003

M.A. Haafeez.

(M.A. HAAFEEZ)
ASST. CONTROLLER OF PATENTS & DESIGNS

FORM 1
THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF A PATENT (Section 5(2),7 and Rule 33A)

We, Glenmark Pharmaceuticals Limited, an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026 INDIA hereby declare

1.(a) that we are in possession of an invention titled **"NOVEL TRICYCLIC COMPOUNDS USEFUL FOR THE TREATMENT OF INFLAMMATORY AND ALLERGIC DISORDERS: PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"**

(b) that the provisional specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are **GOPALAN BALASUBRAMANIAN, LAXMIKANT ATMARAM GHARAT, AFTAB DAWOODBHAI LAKDAWALA, RAGHU RAM ANUPINDI** All citizens & residents of India belonging to Glenmark Pharmaceuticals Limited , B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026

3. that we are the assignee of the true and first inventors

4. that our address for service in India is as follows;

Glenmark Pharmaceuticals Limited
Plot No.A-607, T.T.C Industrial Area
M.I.D.C., Mahape
Navi Mumbai – 400 709
INDIA

5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed) _____
GOPALAN BALASUBRAMANIAN

(Signed) _____
LAXMIKANT ATMARAM GHARAT

(Signed) _____
AFTAB DAWOODBHAI LAKDAWALA

(Signed) _____
RAGHU RAM ANUPINDI

DUPLICATE

भारत सरकार पेटेन्ट कार्यालय शाखा
23 OCT 2002
मुंबई - ४०० ०१२.

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. following are the attachments with the application
(a) Provisional Specification (40 pages, in triplicate)
(b) Fee Rs. 5000.00 (five thousand rupees only) in bank draft bearing No. 007972 dated 21 October, 2002, drawn on UTI Bank Ltd

We request that a patent may be granted to us for the said invention

Dated this Twenty third (23rd) day of October 2002

CHERYL PINTO
Director
Glenmark Pharmaceuticals Limited

To,
The Controller of Patents
The Patents Office Branch, Mumbai

922 | मुंबई MUM | 2002
23 OCT 2002

FORM 2

THE PATENTS ACT 1970
(Act 39 of 1970)

PROVISIONAL SPECIFICATION

(SECTION 10)

NOVEL TRICYCLIC COMPOUNDS USEFUL FOR THE TREATMENT OF INFLAMMATORY AND ALLERGIC DISORDERS: PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

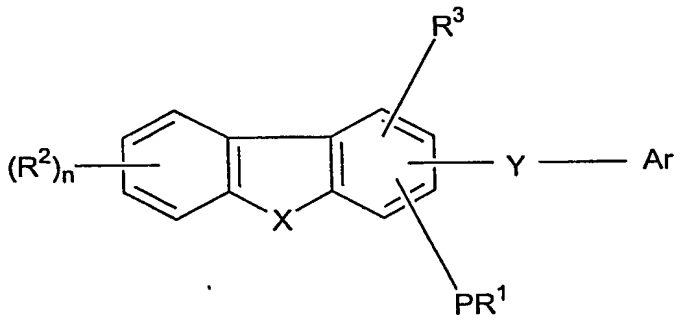
Glenmark Pharmaceuticals Limited, an Indian Company,
registered under the Indian company's Act 1957 and
having its registered office at

B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road
Post Box No. 26511
Mumbai - 400 026, India

THE FOLLOWING SPECIFICATION DESCRIBES THE NATURE OF THE INVENTION.

Field of the Invention

The present invention relates to novel heterocyclic compounds, their analogs, their tautomers, their regioisomers, their stereoisomers, their enantiomers, their diastreomers, their polymorphs, their pharmaceutically acceptable salts, their appropriate oxides, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them. The present invention more particularly relates to novel PDE4 inhibitors of the formula (1), their analogs, their tautomers, their enantiomers, their diasteromers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their appropriate oxides, their pharmaceutically acceptable solvates and the pharmaceutical compositions containing them.



(1)

The invention thus relates to compounds of the formula (1), in which

R^1, R^2 and R^3 may be same or different and are independently selected from the groups consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-C(O)-R^1$, $-C(O)O-R^1$, $-C(O)NR^1R^1$, $-S(O)_m-R^1$, $-S(O)_m-NR^1R^1$, nitro, -OH, cyano, amino, formyl, halogen,$-OR^1$, SR^1 or two R^2 substituents may form a carbocylic ring;

wherein P represents direct bond, oxygen, sulfur or NR^1;

wherein n represents 0 – 4;

Ar is substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

Preferably Ar is optionally substituted phenyl or optionally substituted pyridyl in which optional substituents may be same or different and are independently selected from the groups consisting of hydroxyl, halogen, cyano, carboxyl, trifluoroalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylcarbonyloxy, amino, mono or di substituted or unsubstituted alkylamino, hydrogen, cyano or carboxyl,

the salts of these compounds, and the N-oxides of the pyridines and their salts.

X is oxygen, $S(O)_m$ or NR^1;

Wherein m is 0, 1 or 2;

Y is $-CONR^4$, $-NR^4SO_2$, $-SO_2NR^4$ or $-NR^4CO$;

R^4 is hydrogen, substituted or unsubstituted alkyl, hydroxyl, $-OR^1$, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic ring ;

The substituents in the 'substituted alkyl', 'substituted alkenyl' ' substituted alkynyl' 'substituted cycloalkyl' substituted cycloalkylalkyl' substituted cyclocalkenyl' 'substituted arylalkyl' 'substituted aryl' 'substituted heterocyclic ring', 'substituted heteroaryl ring,' 'substituted heteroarylalkyl', 'substituted heterocyclylalkyl ring' and 'substituted carboxylic acid' may be the same or different which one or more selected from the groups such as hydrogen, hydroxy, halogen, carboxyl, cyano, amino, nitro, oxo (=O), thio (=S), formyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, aryl, heteroaryl, heterocyclic ring, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-N(R^x)CO-$, $-(=N-N(R^x)R^y)$, $-N(R^x)R^yCO-$, $-NR^xR^yC(O)OR^z$, $-NR^xR^y$, $-NR^xC(O)R^y-$, $-NR^xC(S)R^y$ -, $-NR^xC(S)NR^yR^z$, $-N(R^x)SO-$, $-NR^xSO_2-$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y-$, $-OC(O)R^x$, $-OC(S)R^x-$, $-OC(O)OR^x-$, $-OC(O)NR^xR^y$, $-R^xNR^yR^z$, $-R^xR^yR^z$, $-R^xCF_3$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, -

$R^xC(O)NR^yR^z$, $-R^xCS$, $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, or $-ONO_2$,(wherein R^x, R^y and R^z in each of the above groups can be hydrogen atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstitued heterocyclic ring, substituted or unsubstitued heterocyclylalkyl, substituted or unsubstitued heteroaryl or substituted or unsubstitued heteroarylalkyl)

The present invention also relates to a process for the preparation of the above said novel heterocyclic compounds of the formula (1) as defined above. The compounds of general formula (1), more particularly, down regulate or inhibit the production of TNF-α as they are PDE4 inhibitors and therefore are useful in the treatment of variety of allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjuctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. The compounds of the present invention are particularly useful for the treatment of asthma.

Back ground of the Invention

Airway inflammation characterizes a number of severe lung diseases including asthma and chronic obstructive pulmonary disease (COPD). Events leading to airway obstruction include edema of airway walls, infiltration of inflammatory cells into the lung, production of various inflammatory mediators and increased mucous production. The airways of asthmatic patients are infiltrated by inflammatory leukocytes, of which the eosinophil is the most prominent component. The magnitude of asthmatic reactions is correlated with the number of eosinophils present in lungs.

The accumulation of eosinophils is found dramatically in the lungs of asthmatic patients although they are very few in the lungs of a normal individual. They are capable of lysing and activating cells and destroying tissues. When activated, they synthesize and release inflammatory cytokines such as IL-1, IL-3, TNF-α and inflammatory mediators

such as PAF, LTD4 and relative oxygen species that can produce edema, bronchoconstriction. Tumor necrosis factor (TNF-α) was also known to be involved in the pathogenesis of a number of autoimmune and inflammatory diseases. Consequently, manipulation of the cytokine signaling or biosynthetic pathways associated with these proteins may provide therapeutic benefit in those disease states. It has been well demonstrated that TNF-α production in pro-inflammatory cells becomes attenuated by an elevation of intracellular cyclic adenosine 3',5'-monophosphate(cAMP). This second messenger is regulated by the phosphodiesterase(PDE) family of enzymes. The phosphodiesterase enzymes play an integral role in cell signaling mechanisms by hydrolyzing cAMP and cGMP to their inactive 5' forms. Inhibition of PDE enzymes thus results in an elevation of cAMP and /or cGMP levels and alters intracellular responses to extra cellular signals by affecting the processes mediated by cyclic nucleotides. Since eosinophilis are believed to be a critical proinflammatory target for asthma, identification of the expression of PDE 4 gene family in eosinophils led to the PDE 4 as potential therapeutic target for asthma [Rogers.D.F., Giembycz.M.A., *Trends Pharmacol. Sci.*, 19, 160-164(1998); Barnes,P.J., *Trends Pharmacol.Sci.*, 19,415-423(1998)].

The mammalian cyclic nucleotide phosphodiesterases(PDEs) are classified into ten families on the basis of their amino acid sequences and/or DNA sequence, substrate specificity and sensitivity to pharmacological agents [Soderling,S.H., Bayuga,S.J., and Beavo,J.A., *Proc. Natl. Acad. Sci., USA*,96,7071-7076(1999); Fujishige, K, Kotera, J., Michibata, H., Yuasa, K., Takebayashi,Si, Okamura,K. and Omori,K., *J.Biol.Chem.*,.,274, 18438-18445(1999)]. Many cell types express more than one PDE and distribution of isoenzymes between the cells varies markedly. Therefore development of highly isoenzyme selective PDE inhibitors provide a unique opportunity for selective manipulation of various pathophysiological processes.

Phosphodiesterase type 4 (PDE4) is an enzyme which regulates activities in cells which lead to inflammation in the lungs. PDE4, a cAMP-specific and Ca^{+2}-independent enzyme, is a key isozyme in the hydrolysis of cAMP in mast cells, basophils, eosinophils, monocytes and lymphocytes. The association between cAMP elevation in inflammatory

cells with airway smooth muscle relaxation and inhibition of mediator release has led to widespread interest in the design of PDE4 inhibitors[Trophy,T.J., *Am.J.Respir.Crit.Care Med.*, 157, 351-370(1998)]. Excessive or unregulated TNF-α production has been implicated in mediating or exacerbating a number of undesirable physiological conditions such as diseases including osteoarthritis, and other arthritic conditions; septic, shock, ecdotoxic shock, respiratory distress syndrome, bone resorption diseases ; Since TNF-α also participates in the onset and progress of autoimmune diseases, PDE4 inhibitors may find tremendous utility as therapeutic agents for rheumatoid arthritis, multiple sclerosis and Crohn's disease. [*Nature Medicine*, 1, 211-214(19195) and *ibid.*, 244-248]. TNF-α is also reported to be a factor of insulin-resistant diabetes because it declines the phosphorylating mechanism of insulin receptors of muscle and fat cells [*J.clin.Invest.*, 94, 1543-1549(1994)].

Interest in the drugs capable of selective inhibition of PDE 4 has taken much attention due to several factors such as (a) the tissue distribution of PDE-4 strongly suggested that the pathologies related to the central nervous and immune systems could be treated through the selective PDE 4 inhibitors (b) the increase in intracellular cAMP concentration, the obvious biochemical consequence of PDE-4 inhibition, has been well characterized in immuno-competent cells where it acts as a deactivating signal.

Recently four human cDNA isoforms of PDE-4 (PDE4-A,B,C,D) were identified. mRNA for all these four isoforms was expressed in human lungs. PDE 4-A, B and D were expressed in eosinophils. Of these gene families, PDE-4 characterized as the cAMP-specific gene family has been shown to predominate in pro-inflammatory human lymphoid and myeloid lineage cells.

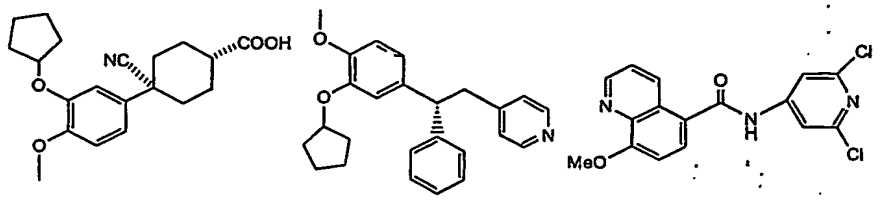
It has been demonstrated that increasing cAMP levels within these cells results in suppression of cell activation which in turn inhibits the production and release of pro-inflammatory cytokines such as TNF-a. Since eosinophilis are believed to be a critical pro-inflammatory target for asthma, identification of the expression of PDE 4 gene family in cosinophils led to the PDE 4 as potential therapeutic target for asthma.

OBJECTIVE OF THE INVENTION

The usefulness of several PDE 4 inhibitors, unfortunately, is limited due to their undesirable side effect profile which include nausea and emesis (due to action on PDE4 in CNS) and gastric acid secretion due to action on PDE4 in parietal cells in the gut.[Barnette, M.S., Grous, M., Cieslinsky, L.B.,Burman,M., Christensen,S.B., Trophy,T.J.,*J. Pharmacol.Exp.Ther.*,273,1396-1402(1995)]. One of the earliest PDE4 inhibitor, Rolipram, was withdrawn from the clinical development because of its severe unacceptable side effect profile.[Zeller E.et.al.,*Pharmacopsychiatr.*, 17, 188-190(1984)]. It has recently become apparent, to some extent. The cause of severe side effects of several PDE4 inhibitor molecules in human clinical trials has recently become apparent.

There exists two binding sites on mammalian PDE4 at which inhibitor molecules bind. Also PDE4 exists in two distinct forms which represent different conformations. They are designated as High affinity Rolipram binding site PDE4H and Low affinity Rolipram binding site PDE4L[Jacobitz,S., McLaughlin,M.M., Livi,G.P., Burman,M., Trophy,T.J., *Mol.Pharmacol* .,50, 891-899(1996)]. It was proved that certain side effects (vomiting and gastric acid secretion) are associated with inhibition of PDE4H whereas some beneficial actions are associated with PDE4L inhibition. It was also found that human recombinant PDE4 exists in 4 isoforms A, B, C and D[Muller,T., Engels,P., Fozard,J.R., *Trends Pharmacol. Sci.*, 17, 294-298(1996)]. Accordingly compounds displaying more PDE4D isoenzyme selectivity over the A, B or C are found to have less amount of side effects than Rolipram [Hughes. B et.al.,, *Br. J. Pharmacol.* **1996**, 118, 1183-1191]. Therefore selective inhibitors of PDE4 isozymes would have therapeutic effects in inflammatory diseases such as asthma and other respiratory diseases.

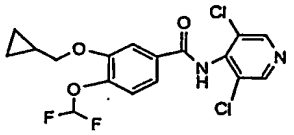
Although several research groups all over the world are working in this direction for achieving the desired highly selective PDE4 isozyme inhibitors, so far the success is limited. Among the various compounds which showed clinically proven PDE 4 inhibition,



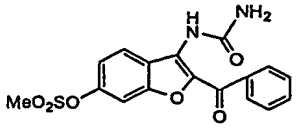
ARIFLO 2

CDP-840 3

D-4418 4

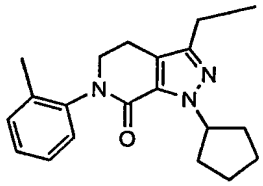


Roflumilast 5

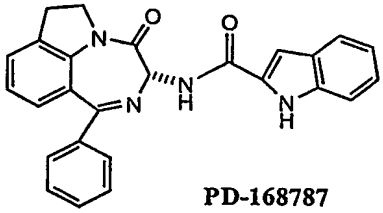


Bay-19-8004 6

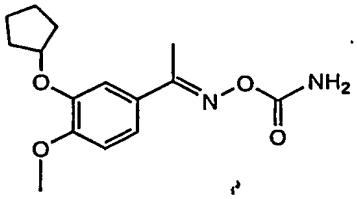
'Ariflo" of the formula 2(Smith Kline Beecham's compound), Byk Gulden's Roflumilast of formula 5 and Bayer's Bay-19-8004 of formula 6 have reached advanced stage of human clinical trials. Some of the other compounds which have shown potent PDE4 inhibitory activity are CDP-840 of the formula 3 (Cellthech's compond), D-4418 of the formula 4 (Schering-Plough's compound), 5CP-220,629 of the formula 7 (Pfizer's) , PD-168787 of the formula 8 (Parke-Davis's compound) and Filaminast of the formula 9 (American Home Products' compound). However, recently due to various reasons such as efficacy and side effects problems, Ariflo, CDP-840 and Bay-19-8004 were discontinued from clinical trials for asthma treatment. Other compounds of the formulae 4 and 7 are presently undergoing phase-1 clinical trials.



CP - 220,629
7



PD-168787
8



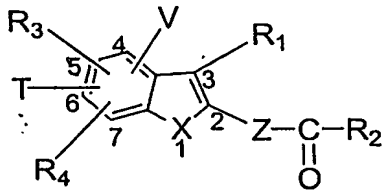
Filaminast
9

During the course of research aimed at the development of novel anti-asthmatic compounds having potential PDE4 inhibitory activity, we have found in the literature

1) US 4,933,351 granted patent (Issued on June 12, 1990 to Merck Frosst Canada Inc.,)

Benzofuran 2-carboxy amides useful as inhibitors of leukoriene biosynthesis

One embodiment of the present invention is pharmaceutical composition containing a compound of the formula I and acceptable pharmaceutical carrier:



(I)

wherein :

Z is a bond, $CR_{14}=CR_{15}$;

X is O, S, So or SO_2;

R_2 is H, OH,C_1 toC_{20} alkoxy, including straight chain or branched chain, cycloalkyl, bicycloalkyl, tricycloalkyl or tetracycloalkyl ;

Ar_1-C_1 toC_3 alkoxy;

NR_8Ar_1, wherein R_8 and Ar_1 can optionally be joined to form a heterocyclic ring having 5 to 8 atoms;

-NR_8Het;

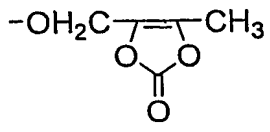
-$N(R_8)CH_2Ar_1$

-$N(R_{13})$-$N(R_{13})_2$ wherein R_{13} is independently hydrogen, R_8, R_9,Ar_1 or Het:

-NH-CH=$C(Ar_1)_2$;

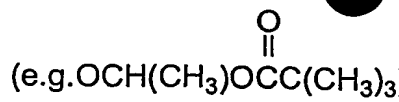
-$O(CH_2)_nNR_8R_9$ wherein N is 2 to 4;

-Z-Ar_1;



;

lower acyloxy-lower alkoxy



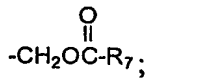
-CH_2OH;

-$(CH_2)_nAr_1$ wherein in n is 0 to 3;

-$(CH_2)_nCOOR_6$ wherein n is 0 to 6;

C_1 toC_{20} alkyl; Ar_1; Het; $(CH_2)_nNR_8R_9$

Wherein n is 1 to 3; or Het;



and R_1, R_3 R_4, T and V are independently selected from

1. hydrogen;
2. alkyl having 1 to 6 carbon atoms;
3. alkenyl having 2 to 6 carbon atoms;
4. -$(CH_2)_nM$ wherein n is 0 to 6 except when X is S and M is oR_5, in which n is 1 to 6 and M is

a) -OR_5;

b) halogen;

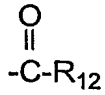
c) -CF_3;

d) -SR_5;

e) Ar_1;

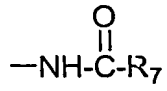
f)-$COOR_6$;

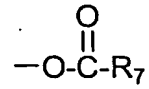
g)

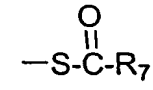


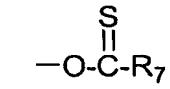
Wherein R_{12} is H , C_1 to C_6 alkyl, or Ar_1;

h) tetrazole;

i) 

j) 

k) 

l) 

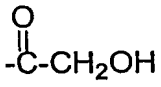
m)

$-NR_8R_{10}$

n)

$-NHSO_2R_{10}$ Wherein R_{10} is OH, C_1 toC_6 alkyl, CF_3, C_1 to C_6 alkoxy, or Ar;

o)



p) $-SOR_5$

q)$-CONR_8R_9$;

r) $-SO_2NR_8R_9$;

s) $-SO_2R_5$;

t) $-NO_2$; or

u) –CN

or any two of R_3,R_4,T and V may be joined to form a saturated ring having 5 to 6 ring atoms, said ring atoms comprising 0,1 or 2atoms selected from oxygen and sulfur, the remaining ring atoms been carbon;

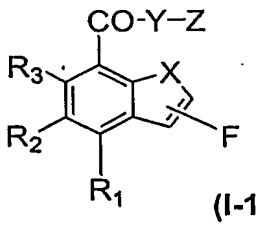
each R_5 is independently H, C_1 to C_6 alkyl, benzene, Ar_1, perfluro-C_1 toC_4 alkyl, CH_2-R_{11} is C_1 toC_5 alkyldimethylamino,hydroxyl-C_2 toC_5 alkyl, CH_2COOR_6, or CH_2CO-R_7;

each R_6 is independently H, or C_1 to C_6 alkyl;

each R_7 is independently C_1 to C_6 alkyl, benzyl,Ar_1,NR_8R_9, $NHAr_1$ or O-C_1 toC_4 alkyl;
each R_8 and R_9 is independently H or C_1 to C_4 alkyl, or R_8 and R_9 may be joined through the N to which they are attached to form a heterocycloalkyl ring having 5 to 8 ring atoms;
each Het is independently an aromatic heterocyclic ring having 5 to 6 ring atoms,one or more of which is selected from N, O and S;
each Ar_1 is independently 1- or 2-naphtyl,phenyl or mono- or disubstituted phenyl, wherein the substituents on phenyl are independently selected from C_1 to C_3 alkyl, I Br, Cl, F, $COOR_6$,$(CH_2)_n$-NR_8R_9 wherein n is 0 to2, methylenedioxy,C_1 to C_3 alkoxy, OH, CN,NO_2, CF_3, C_1 toC_4 acyl, NR_8R_9, S-C_1 to C_6 alkyl, SO-C_1 toC_6 alkyl, and SO_2-C_1 to C_6 alkyl; and R_{14} and R_{15} are each independently H, C_1 toC_6 alkyl; or a pharmaceutically acceptable salts thereof

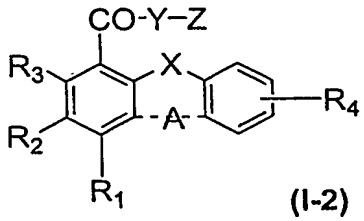
2) PCT Patent publication WO 94/08995 (published on April 28, 1994 by Smithkline Beecham Plc)

Heterocyclic condensed benzoic acid derivatives as 5-HT4 receptor antagonists
Compound of formula (I) or a pharmaceutically accepted salts there of:



(I-1)

Wherein X is O, or S;
R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxyl or C_{1-6} alkoxy;
R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, or C_{1-6} alkylthio;
R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or amino;
R_4 is hydrogen or C_{1-6} alkyl;



(I-2)

Wherein

X is O or S

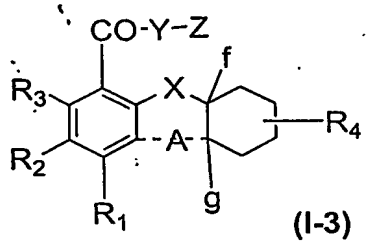
A represent a single bond,-CH_2- or CO or A is $(CH_2)_a$-E-$(CH_2)_b$ where one of a and b is 0 and the other is 0 or 1 and E is O,S or NH;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxyl or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, or C_{1-6} alkylthio;

R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or amino;

R_4 is hydrogen or C_{1-6} alkyl;



(I-3)

Wherein

X is O or S

A represent a single bond,-CH_2- or CO or A is $(CH_2)_a$-E-$(CH_2)_b$ where one of a and b is 0 and the other is 0 or 1 and E is O,S or NH;

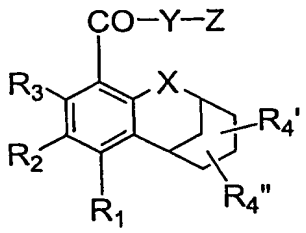
f and g are both hydrogen or together are a bond;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxyl or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, or C_{1-6} alkylthio;

R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or amino;

R_4 is hydrogen or C_{1-6} alkyl;



(I-4)

Wherein

X is O or S;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxyl or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, or C_{1-6} alkylthio;

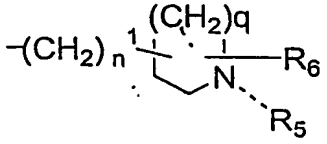
R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or amino;

R_4^{I} and R_4^{II} are independently hydrogen or C_{1-6} alkyl;

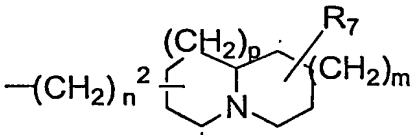
In formulae (I-1) to (I-4) inclusive:

Y is O or NH;

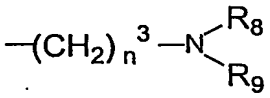
Z is of sub-formula (a), (b) or (c):



(a)



(b)



(C)

Wherein n^1 is 0,1,2,3 or 4; n^2 is 0,1,2,3 or 4; n^3 is 2,3,4 or 5;

q is 0,1,2 or 3; p is 0,1 or 2; m is 0,1 or 2;

R_5 is hydrogen, C_{1-12} alkyl, aralkyl or R_5 is $(CH_2)_z$-R_{10} wherein z is 2 or3 and R_{10} is selected from cyano, hydroxyl, C_{1-6} alkoxy, phenoxy, $C(O)C_{1-6}$ alkyl, COC_6H_5, -$CONR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$ or $NR_{11}SO_2R_{12}$, wherein R_{11} and R_{12} are hydrogen or C_{1-6} alkyl; and

R_6, R_7 and R_8 are independently hydrogen or C_{1-6} alkyl; and

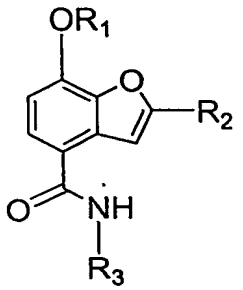
R_9 is hydrogen or C_{1-10} alkyl;

or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere;

3) PCT Patent publication WO 01/58895-A1 (published on August 16, 2001 by Darwin Discovery Limited)

This invention provides novel compounds having therapeutic utility, in particular for the treatment of disease states associated with proteins which mediate cellular activity, for

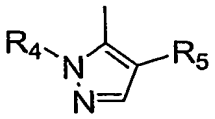
example by inhibiting TNF and / or PDE-IV. According to the invention, the compounds of formula (i):



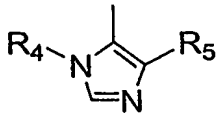
wherein R_1 is C_{1-3} alkyl optionally substituted with one or more fluorines;

R_2 is CH_2OCH_3 or 2 or 3–tetrahydrofuranyl;

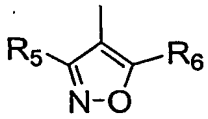
R_3 is a pyrazole, imidazole or isoxazole group of a partial formula (A), (B) or (C)



(A)



(B)



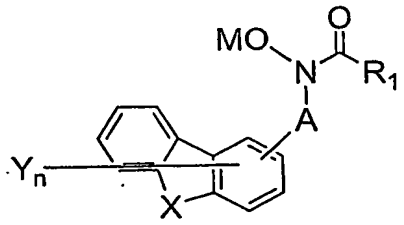
(C)

R_4 is C_{1-3} alkyl; and

R_5 and R_6, which may be same or different, each represents C_{1-3} alkyl, halogen, CF_3 or CN;

4) US granted patent 4,769, 387 (Issued on September 06, 1988 to Abbott Laboratories)

In accordance with the present invention, there are 5-and / or 12-lipoxygenase inhibiting compounds of the formula:



wherein R is (1) hydrogen, (2) C_1 to C_4 alkyl, (3) C_2 to C_4 alkenyl, or (4) NR_2R_3, wherein R_2 and R_3 are independently selected from hydrogen, C_1 to C_4 alkyl or hydroxyl, but R_2 and R_3 are not simultaneously hydroxyl;

X (1) oxygen, (2) sulfur, (3) SO_2, or (4) NR_4 wherein R_4 is (1) hydrogen, (2) C_1 toC_6 alkyl, (3) C_1 to C_6 alkoyl, or (4) aroyl;

A is selected from C_1 to C_6 alkylene and C_2 to C_6 alkenylene;

Y is selected independently at each occurrence from (1) hydrogen, (2) halogen, (3) hydroxy, (4) cyano (5) halosubstituted alkyl, (6) C_1 to C_{12} alkyl, (7) C_2 to C_{12} alkenyl, (8) C_1 to C_{12} alkoxy, (9) C_3 to C_8 cycloalkyl, (10) aryl, (11) aryloxy, (12) aroyl, (13) C_1 to C_{12} arylalkyl, (14) C_2 to C_{12} arylalkenyl, (15) C_1 to C_{12} arylalkoxy, (16) C_1 to C_{12} arylthioalkoxy, and substituted derivatives of (17) aryl, (18) aryl-oxy, (19) aroyl, (20) C_1 to C_{12} arylalkyl, (21) C_2 to C_{12} arylalkenyl, (22) C_1 toC_{12} arylalkoxy, or (23) C_1 to C_{12} arylthioalkoxy, wherein substituents are selected from halo, nitro, cyano C_1 toC_{12} alkyl, alkoxy, and halosubstituted alkyl; the number n is 0–4; the group(s) Y may be substituted from any of the positions on the aryl rings;

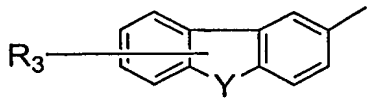
and M is hydrogen, a pharmaceutically acceptable cation, aroyl, or C_1 to C_{12} alkoyl.

5) US granted patent US 3, 897,453 (Issued on July 29, 1975 to Merck Patent Gesellschaft mitbeschrankter Haftung)

The novel compounds of the invention are dibenzofuran and dibenzothiophene derivatives of the general formula I

$$Z\text{-}CHR_1R_2 \qquad (I)$$

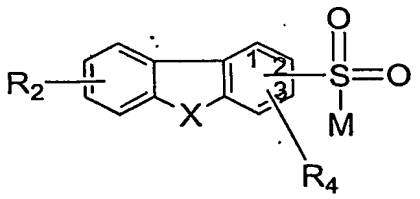
In which Z is



wherein R_1 is COOH, CHO, or CH_2OH including functional derivatives thereof; R_2 is H or alkyl of 1-4 carbon atoms; R_3 is H, alkyl, alkoxy, alkanoyl, monoalkylamino, dialkylamino, or acylamino, each of up to 4 carbon atoms, F, Cl, Br, I, OH, NH_2, NO_2, CN, or CF_3; and Y is O or S; with the proviso that at least one of R_2 and R_3 is other than H; and the physiologically acceptable salts thereof.

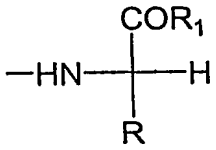
6) PCT Publication WO 98/09934 (Published on March 12; 1998 by Warner Lambert)

The present invention provides a method of inhibiting a matrix metalloproteinase in a patient in need of matrix metalloproteinase inhibition comprising administering to the patient a therapeutically effective amount of the compound of formula I



I

Wherein M is a natural (L) alpha amino acid derivative having the structure



X is O, S, $S(O)_n$, CH_2, CO, or NR_Q;

R_Q is hydrogen, C_1-C_6 alkyl or –C_1-C_6 alkyl-phenyl; R is aside chain of a natural alpha amino acid;

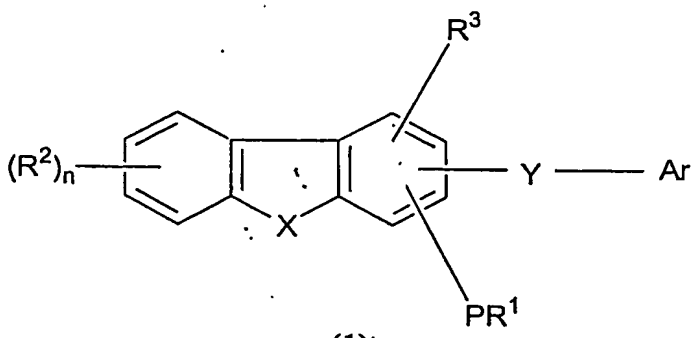
R_1 is C_1-C_5 alkoxy, hydroxy, or –$NHOR_5$;

R_2 and R_4 are independently hydrogen, –C_1-C_5 alkyl, phenyl-NO_2, halogen, -OR_5, -CN, -CO_2R_5, -SO_3R_5, -CHO, -COR_5, -$CONR_5R_6$,-$(CH_2)_nNR_5R_6$, -CF_3, or -$NHCOR_5$;

Each R_5 and R_6 are independently hydrogen, C_1-C_5 alkyl; and n is 0 to 2, and the pharmaceutically acceptable salts, esters, amides and prodrugs thereof.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides novel heterocyclic compounds of the general formula **(1)**



(1)

The invention thus relates to compounds of the formula **(1)**, in which

R^1, R^2 and R^3 may be same or different and are independently selected from the groups consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstitued alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , -C(O)-R^1, -C(O)O-R^1, -C(O)NR^1R^1 , -$S(O)_m$-R^1, -$S(O)_m$-NR^1R^1 , nitro, -OH, cyano, amino, formyl, halogen,-OR^1, SR^1 or two R^2 substituents may form a carbocyclic ring;

wherein P represents direct bond, oxygen, sulfur or NR^1;

wherein n represents 0 – 4;

Ar is substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

Preferably Ar is optionally substituted phenyl or optionally substituted pyridyl in which optional substituents may be same or different and are independently selected from the groups consisting of hydroxyl, halogen, cyano, carboxyl, trifluoroalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted

alkylcarbonyloxy, amino, mono or di substituted or unsubstituted alkylamino, hydrogen, cyano or carboxyl,

the salts of these compounds, and the N-oxides of the pyridines and their salts.

X is oxygen, $S(O)_m$ or NR^1;

Wherein m is 0, 1 or 2;

Y is $-CONR^4$, $-NR^4SO_2$, $-SO_2NR^4$ or $-NR^4CO$;

R^4 is hydrogen, substituted or unsubstituted alkyl, hydroxyl, $-OR^1$, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic ring ;

The substituents in the 'substituted alkyl', 'substituted alkenyl' ' substituted alkynyl' 'substituted cycloalkyl' substituted cycloalkylalkyl' substituted cyclocalkenyl' 'substituted arylalkyl' substituted aryl, 'substituted heterocyclic ring', 'substituted heteroaryl ring,' 'substituted heteroarylalkyl', 'substituted heterocyclylalkyl ring' and 'substituted carboxylic acid' may be the same or different which one or more selected from the groups such as hydrogen, hydroxy, halogen, carboxyl, cyano, amino, nitro, oxo (=O), thio (=S), formyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, aryl, heteroaryl, heterocyclic ring, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-N(R^x)CO-$, $-(=N-N(R^x)R^y)$, $-N(R^x)R^yCO-$, $-NR^xR^yC(O)OR^z$, $-NR^xR^y$, $-NR^xC(O)R^y-$, $-NR^xC(S)R^y$ -, $-NR^xC(S)NR^yR^z$, $-N(R^x)SO-$, $-NR^xSO_2-$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y-$, $-OC(O)R^x$, $-OC(S)R^x-$, $-OC(O)OR^x-$, $-OC(O)NR^xR^y$, $-R^xNR^yR^z$, $-R^xR^yR^z$, $-R^xCF_3$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xCS$, $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, or $-ONO_2$,(wherein R^x, R^y and R^z in each of the above groups can be hydrogen atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstitued heterocyclic ring, substituted or unsubstitued heterocyclylalkyl, substituted or unsubstitued heteroaryl or substituted or unsubstitued heteroarylalkyl)

DETAILED DESCRIPTION OF THE INVENTION

The term 'alkyl' refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl), and the like .

The term "Alkenyl " refers to aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched or branched chain having about 2 to about 10 carbon atoms in the e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term " Alkynyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 10 carbon atoms presently being preferred) e.g., ethynyl, propynyl, butnyl and the like.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of about 3 to 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and examples of multicycic cycloalkyl groups include perhydronaphthyl, adamantyl and norbornyl groups and sprirobicyclic groups e.g sprio (4,4) non-2-yl.

The term " cycloalkylalkyl" refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms directly attached to alkyl group which then attached to the main structure at any carbon from alkyl group that results in the creation of a stable structure. such as cyclopropylmethyl, cyclobuylethyl, cyclopentylethyl, and the like.

The term " cycloalkenyl" refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms with atleast one carbon- carbon double bond such as cyclopropenyl, cyclobutenyl, cyclopentenyl and the like.

The term "aryl" refers to aromatic radicals having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, tetrahydronapthyl, indanyl, biphenyl and the like.

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above. e.g., $-CH_2C_6H_5$, $-C_2H_5C_6H_5$ and the like.

The term "Heterocyclic ring" refers to a stable 3- to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purpose of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofurnyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl, tetrahydroisouinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxasolidinyl, triazolyl, indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurtyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl , oxadiazolyl , chromanyl, isochromanyl and the like.

The term "Heteroaryl" refers to heterocyclic ring radical as defined above. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "Heteroarylalkyl" refers to heteroaryl ring radical as defined above directly bonded to alkyl group. The heteroarylalkyl radical may be attached to the main

structure at any carbon atom from alkyl group that results in the creation of a stable structure.

The term "Heterocyclyl" refers to a heterocylic ring radical as defined above. The heterocylyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "Heterocyclylalkyl" refers to a heterocylic ring radical as defined above directly bonded to alkyl group. The heterocyclylalkyl radical may be attached to the main structure at carbon atom in the alkyl group that results in the creation of a stable structure.

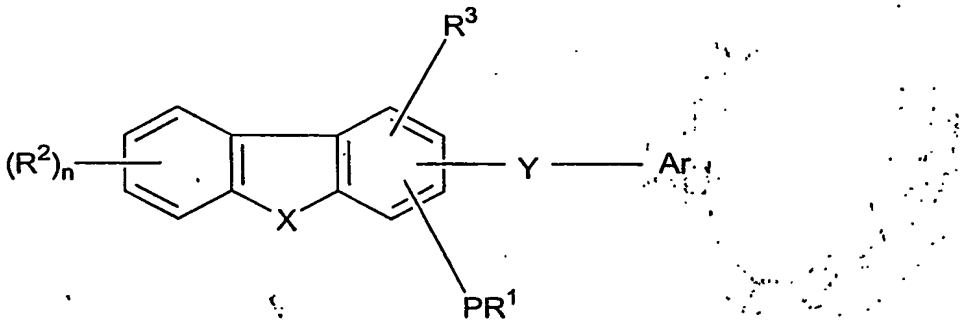
The term "carbocyclic" refers to a cyclic group containing 3-10 carbon atoms

The term "Halogen" refers to radicals of Fluorine, Chlorine, Bromine, Iodine

The term "Pharmaceutical acceptable salts" means non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include acetate, ascorbate, benzenesulfonate, benzoate, bicarbonate, borate, bromide, calcium edetate, carbonate, chloride, citrate, dihydrochloride, edetate, mesylate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxyapthoate, iodide, isothionate, α-ketoglutarate, α-glycerophosphate, glucose-1 phosphate lutarate lactate, lactobionate, laurate, malate, methane-sulphate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, sterate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate.

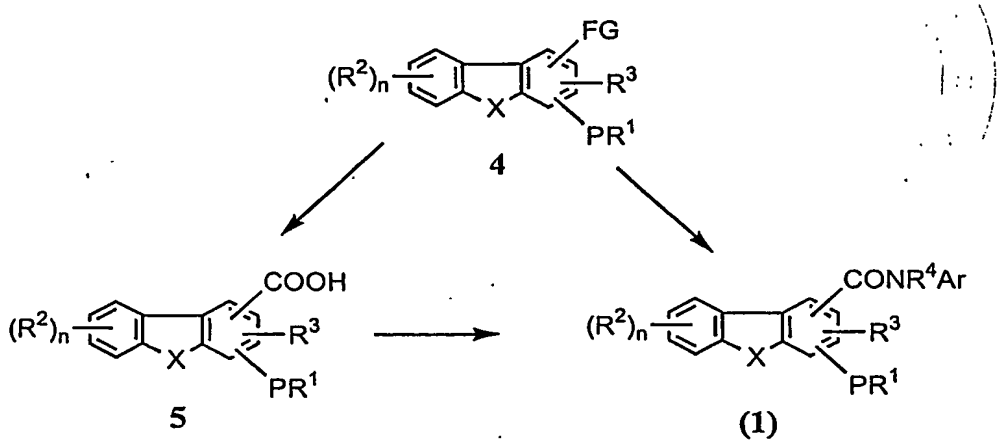
The compounds according to the invention may be prepared by the following processes. The symbols P, Ar, X, Y, R^1, R^2, R^3 and R^4 when used in the below formulae below are to be understood to present those groups described above in relation to formula (1) unless otherwise indicated

The present invention discloses a process for the preparation of compounds of general formula (1).



(1)

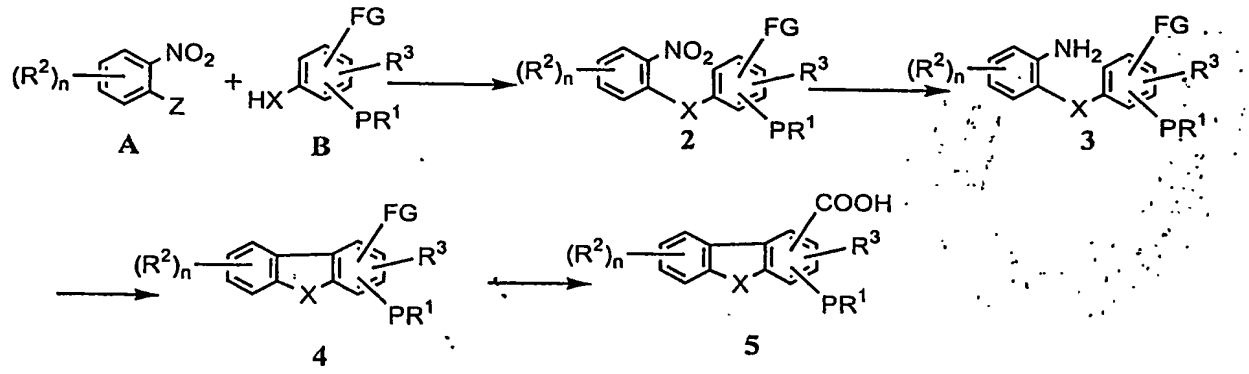
In one embodiment the compounds of the formula (1) where Y is $-CONR^4$, can be prepared by reacting the acid halide or the mixed anhydride of the common intermediate of the formula 4 (wherein FG is COOH) or of the formula 5 (which is obtained from formula 4 wherein FG is alkyl, formyl, cyano, halogen, nitro, amino and the like by conventional methods) with an appropriate amine of the formula $ArNHR^4$ using standard conditions known in the literature.



The common intermediate of the formula 4 and / or of the formula 5 can be synthesized by using any of the general process described in synthetic schemes I to VI.

The desired compounds of the formula (1) obtained are then converted into their salts and/or the N-oxides and, if desired, salts of the compounds of the formula (1) obtained are then converted into the free compounds.

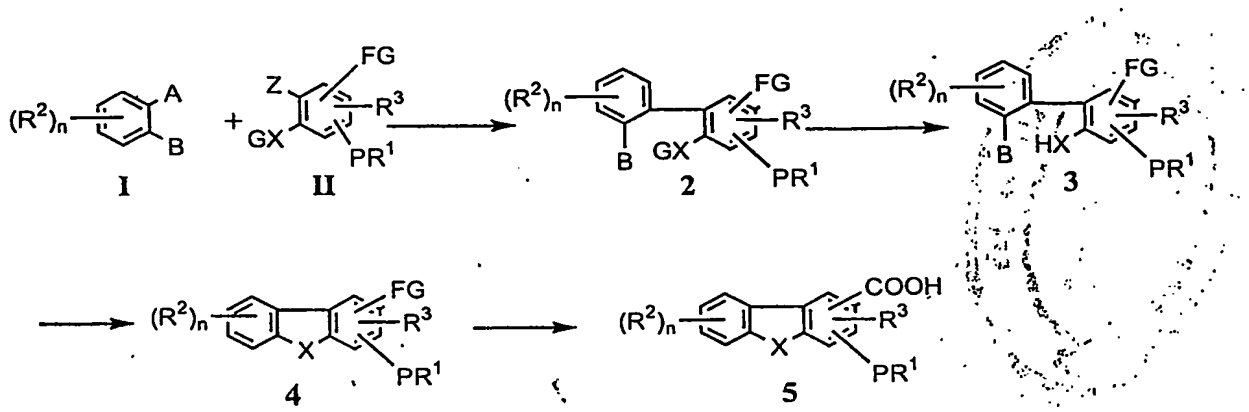
GENERAL SYNTHETIC SCHEME I.



In the above scheme I wherein P, X, R^1, $R^2$and R^3 have the meanings described above intermediate **2** can be synthesized by reacting the appropriate substituted nitrobenzene of the formula **A** (wherein Z is a halogen) with an appropriately substituted or unsubstituted aromatic group of the formula **B** (wherein FG is alkyl, formyl, cyano, halogen, nitro, amino, carboxylic acid group and the like) under appropriate basic conditions. Intermediate **2** can be reduced under standard reducing conditions to the amino compound of the formula **3**. The intermediate **3** can be cyclized to the tricyclic intermediate of the formula **4** by standard diazotization method followed by standard coupling methods. If the functional group FG in **B** is other than the carboxylic acid, then it can be converted to the carboxylic acid at any stage of the synthetic process as permitted by the chemistry of the synthetic process. If in the intermediate of formula **4** FG is alkyl, formyl, cyano, halogen, nitro, amino, then the intermediate **4** can be transformed to the intermediate of formula **5** by conventional methods described in the literature.

Alternatively, the common intermediate of the formula **4** and / or of the formula **5** can be synthesized by the process described in scheme II.

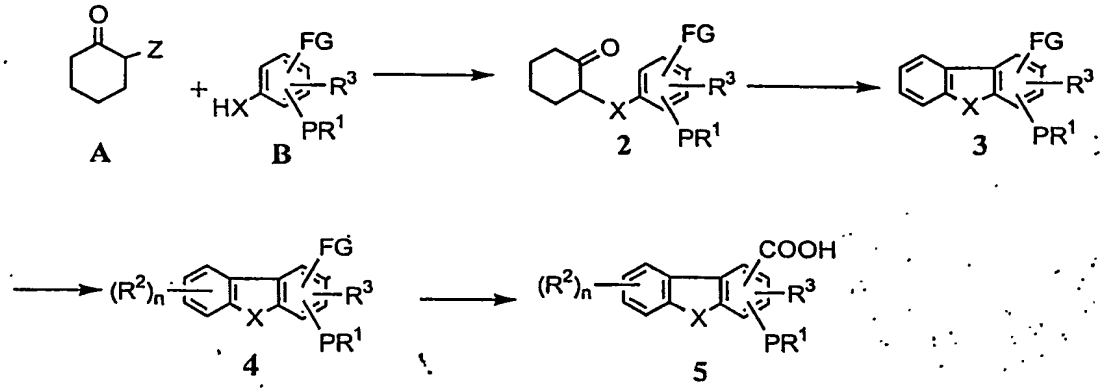
SCHEME II.



In the above scheme II wherein P, X, R^1, $R^2$and R^3 have the meanings described above and wherein A is a halogen, or –OMs or -OTs (Ms = methanesulfonyl group; Ts = p-toluenesulfonyl group) or $-B(OH)_2$, B is a halogen, G is an appropriate protecting group, FG is alkyl, formyl, cyano, halogen, nitro, amino, carboxylic acid group and the like and Z is a halogen intermediate **2** can synthesized by coupling the substituted aryl group of the formula **I** with an appropriately substituted aryl group of formula **II** using standard methods known in the literature. Intermediate **2** can be deprotected to get intermediate **3** which then further cyclized under basic conditions to the tricyclic intermediate of the formula **4**. If the functional group FG in **II** is other than the carboxylic acid, then it can be converted to the carboxylic acid at any stage of the synthetic process as permitted by the chemistry of the synthetic process. If in the intermediate of formula **4** FG is alkyl, formyl, cyano, halogen, nitro, amino, then the intermediate **4** can be transformed to the intermediate of formula **5** by conventional methods described in the literature

Alternatively, the common intermediate of the formula **4** and / or of the formula **5** can be synthesized by the process described in scheme III.

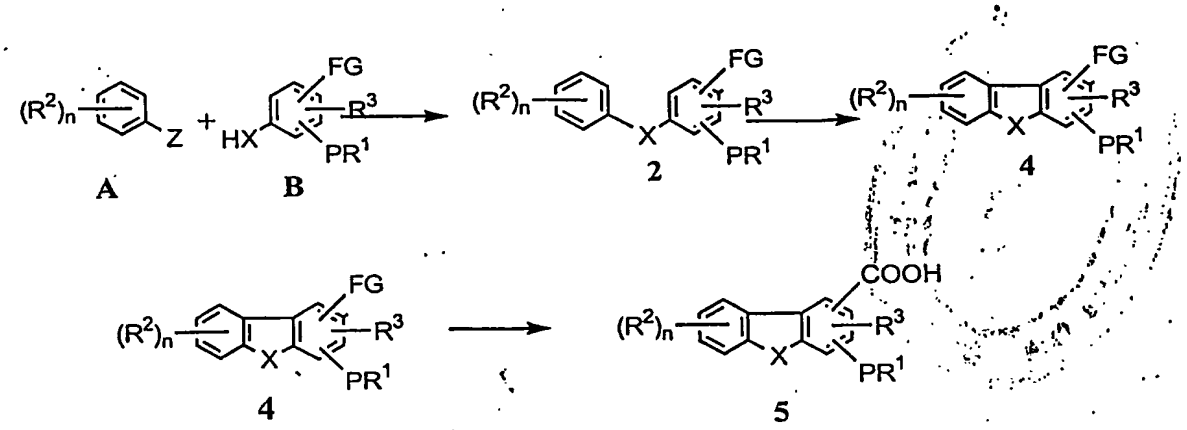
SCHEME III.



In the above scheme III wherein P, X, R^1, $R^2$and R^3 have the meanings described above and wherein Z is a halogen, FG is alkyl, formyl, cyano, halogen, nitro, amino, carboxylic acid group and the like, intermediate **2** can synthesized by reacting the halocyclohexanone of the formula **A** with appropriately substituted aryl group of the formula **B** under standard basic conditions. Intermediate **2** can be cyclized under standard acidic conditions and oxidized to the dibenzofuran intermediate of the formula **3.** The substituents R^2 can be introduced by standard electrophilic substitution reactions described in the literature on intermediate **3** to provide the intermediate of the formula **4.** If the functional group FG in **B** is other than the carboxylic acid, then it can be converted to the carboxylic acid at any stage of the synthetic process as permitted by the chemistry of the synthetic process. If in the intermediate of formula **4** FG is alkyl, formyl, cyano, halogen, nitro, amino, then the intermediate **4** can be transformed to the intermediate of formula **5** by conventional methods described in the literature

Alternatively, the common intermediate of the formula **4** and / or of the formula **5** can be synthesized by the process described in scheme IV.

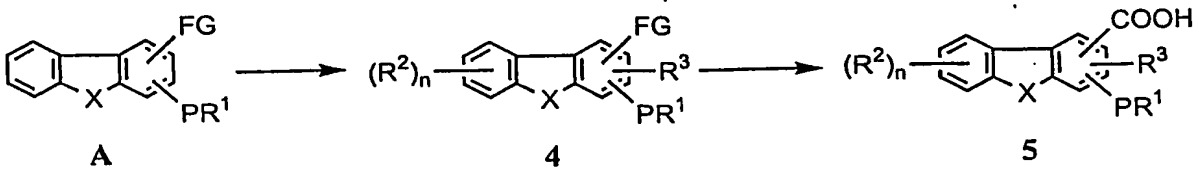
SCHEME IV.



In the above scheme IV wherein P, X, R^1, $R^2$and R^3 have the meanings described above and wherein Z is a halogen, FG is alkyl, formyl, cyano, halogen, nitro, amino, carboxylic acid group and the like, intermediate **2** can synthesized by reacting the substituted aryl group of the formula **A** with appropriately substituted aryl group of the formula **B** under standard basic conditions. Intermediate **2** can be cyclized under standard palladium catalyzed coupling conditions to the dibenzofuran intermediate of the formula **4.** If the functional group FG in **B** is other than the carboxylic acid, then it can be converted to the carboxylic acid at any stage of the synthetic process as permitted by the chemistry of the synthetic process. If in the intermediate of formula **4** FG is alkyl, formyl, cyano, halogen, nitro, amino, then the intermediate **4** can be transformed to the intermediate of formula **5** by conventional methods described in the literature.

Alternatively, the common intermediate of the formula **4** and / or of the formula **5** can be synthesized by the process described in scheme V.

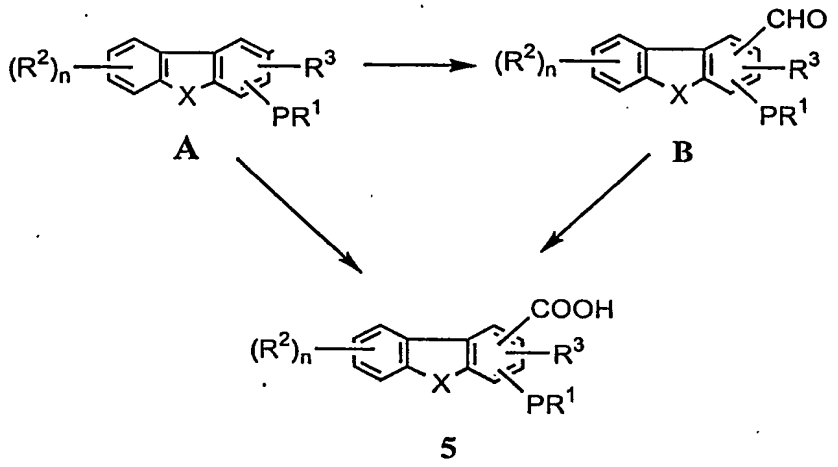
SCHEME V.



In the above scheme V, wherein P, X, R^1, $R^2$and R^3 have the meanings described above and wherein FG is alkyl, formyl, cyano, halogen, nitro, amino, carboxylic acid group and the like, the substituents R^2 and/or R^3 can also be introduced by standard electrophilic substitution reactions on the tricyclic intermediate of the formula A which may be synthesized using any of the above described methods in scheme I, II, III or IV to obtain the desired common intermediates of the formula 4 and/or of the formula 5.

Alternatively, the common intermediate of the formula 5 can be synthesized by the process described in scheme VI.

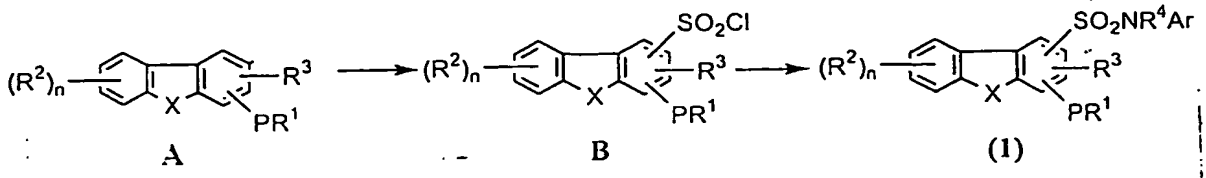
SCHEME VI.



In the above scheme VI wherein P, X, R^1, $R^2$and R^3 have the meanings described above the common intermediate 5 can be synthesized by formylation of intermediate A using standard formylation methods followed by oxidation of the aldehyde group to the carboxylic acid group by conventional methods known in the literature. The common intermediate 5 can also be synthesized directly from the compound of formula A by standard carboxylation methods.

In another embodiment the compounds of the formula (1) where Y is SO_2NR^4, can be synthesized using the process described in scheme VII.

SCHEME VII.

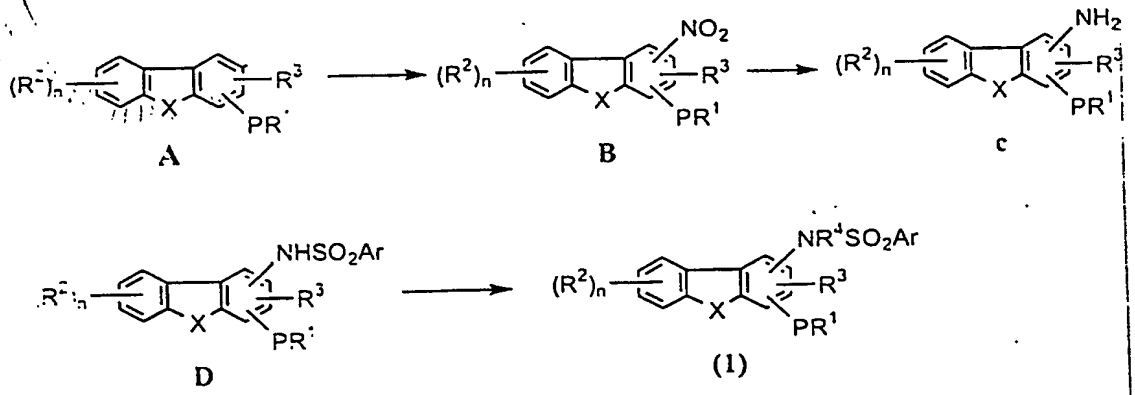


In the above scheme VII wherein P, X, R^1, $R^2$and R^3 have the meanings described above the desired compounds of the formula (1) can prepared by chlorosulfonylation of the compound of formula A to obtain an intermediate of the formula B followed by sulfonamide formation by reacting intermediate B with the amine of the formula $ArNHR^4$ using conventional methods.

If desired compounds of the formula (1) obtained are then converted into their salts and or the N-oxides and, if desired, salts of the compounds of the formula (1) obtained are then converted into the free compounds.

In yet another embodiment the compounds of the formula (1) where Y is NR^4SO_2 can be synthesized using the process described in scheme VIII.

SCHEME VIII.



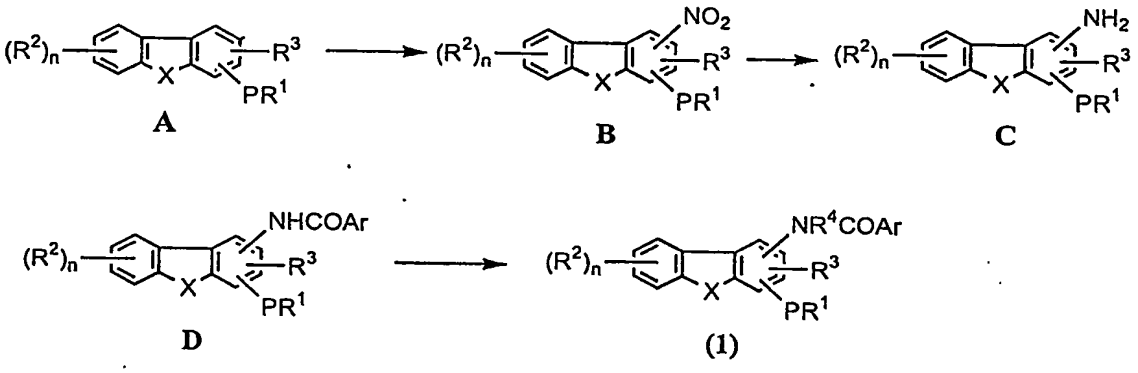
In the above scheme VIII wherein P, X, R^1, $R^2$and R^3 have the meanings described above the desired compounds of the formula (1) can prepared by nitration of the compound of formula A to obtain an intermediate of the formula B followed by

reduction of the nitro to amino group to obtain intermediate **C** using conventional methods. The intermediate **C** can be reacted with appropriate sulfonyl chloride $ArSO_2Cl$ to obtain the sulfonamide **D** which can alkylated to the desired compounds of the formula **(1)** using conventional methods. The sulfonamide **D** is also one of the desired compounds wherein R^4 is hydrogen.

If desired compounds of the formula **(1)** obtained are then converted into their salts and/or the N-oxides and, if desired, salts of the compounds of the formula **(1)** obtained are then converted into the free compounds.

In yet another embodiment the compounds of the formula **(1)** where Y is $-NR^4CO$, can be synthesized using the process described in scheme IX.

SCHEME IX.



In the above scheme IX wherein P, X, R^1, $R^2$and R^3 have the meanings described above the desired compounds of the formula **(1)** can prepared by nitration of the compound of formula **A** to obtain an intermediate of the formula **B** followed by reduction of the nitro to amino group to obtain intermediate **C** using conventional methods. The intermediate **C** can be reacted with appropriate acid chloride of the formula ArCOCl or appropriate mixed anhydride of the formula $ArCOOCOR^5$ (R^5 is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl) to obtain the amide **D** which can alkylated to the desired

compounds of the formula (1) using conventional methods. The amide D is also one of the desired compounds wherein R^4 is hydrogen.

If desired compounds of the formula (1) obtained are then converted into their salts and/or the N-oxides and, if desired, salts of the compounds of the formula (1) obtained are then converted into the free compounds.

The N-oxidation is carried out in a manner likewise familiar to the person skilled in the art, e.g with the aid of m-chloroperoxybenzoic acid in dichloromethane at room temperature. The person skilled in the art is familiar with the reaction conditions which are necessary for carrying out the process on the basis of his expert knowledge.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuum and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent, e.g in a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol (ethanol, isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecepiting, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification or by acidifying into the free compounds which, in turn can be converted into salts.

In general, the ethereal solvents used in the above described processes for the preparation of compounds of the formula (1) are selected from diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran, diisopropyl ether, 1,4 dioxane and the like. The chlorinated solvent which may be employed may be selected from dichloromethane, 1,2-dichloroethane, chloroform, carbontetrachloride and the like . The aromatic solvents which may be employed may be selected from benzene, toluene. The alchoholic solvents

which may be employed may be selected from methanol, ethanol, n-propanol, iso propanol, tert.butanol and the like. The aprotic solvents which may be employed may be selected from N, N-dimethylformamide, dimethyl sulfoxide and the like.

In general, the compounds prepared in the above described processes are obtained in pure form by using well known techniques such as crystallization using solvents such as pentane, diethyl ether, isopropyl ether, chloroform, dichloromethane, ethyl acetate, acetone, methanol, ethanol, iso propanol, water or their combinations, or column chromatography using Alumina or silica gel and eluting the column with solvents such as hexane, petroleum ether (pet.ether), chloroform, ethyl acetate, acetone, methanol or their combinations.

Various polymorphs of a compound of general formula (1) forming part of this invention may be prepared by crystallization of compound of formula (1) under different conditions. example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures, various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The present invention also provides pharmaceutical compositions, containing compounds of the general formula (1) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their enantiomers, their diasteromers, their pharmaceutically acceptable salts or their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like. The pharmaceutical compositions according to this invention can be used for the treatment of allergic disorders.

It will be appreciated that some of the compounds of the general formula (1) defined above according to the invention can contain one or more asymmetrically

substituted carbon atoms. The presence of one or more of these asymmetric centers in the compounds of the general formula (1) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers and their mixtures. including racemic mixtures.

The invention may also contain E & Z geometrical isomers wherever possible in the compounds of the general formula (1) which includes the single isomer or mixture of both the isomers

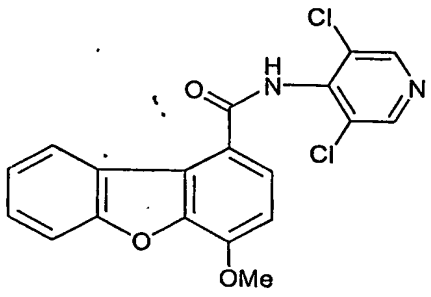
The pharmaceutical compositions may be in the forms normally employed, such as tablets. capsules, powders, syrups, solutions, suspensions and the like and may contain flavorants. sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. The active compounds of the formula (1) will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the compounds of the formula (1) can be combined with a suitable solid, liquid carrier or diluent to form capsules. tablets, powders, syrups, solutions. suspensions and the like. The pharmaceutical compositions. may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral administration, the compounds of the formula (1) can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds of the formula (1). The injectable solutions prepared in this manner can then be administered intravenously. intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

In addition to the compounds of formula (1) the pharmaceutical compositions of the present invention may also contain or be co-administered with one or more known drugs selected from other clinically useful therapeutic agents.

The invention is explained in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

Example 1

N-(3, 5-dichloropyrid-4-yl)-4-methoxy dibenzo[b,d]furan-1-carboxamide



Step 1: 3-(2-nitrophenoxy)-4-methoxy benzaldehyde ; To a stirred suspension of potassium fluoride (5.71 gm, 0.0985 mol) in dry DMSO (20 ml) was added a solution of isovanillin (10.0 gm, 0.0657 mol) in DMSO (20 ml). The reaction contents were heated at 140°C for 10 min. A solution of 2-fluoronitrobenzene (9.27 gm, 0.0657 mol) in DMSO (10 ml) was added to the above suspension and the reaction mixture was stirred at 140°C for 3.5 h. The reaction mixture was cooled to room temperature and the contents were poured into water (200 ml) and extracted with ethyl acetate (100 ml x 3). The organic extracts were combined and washed with 1N sodium hydroxide (50 ml x 2), water and brine and dried over anhydrous sodium sulfate. The dried organic layer was concentrated in vaccuo to obtain the product as a pale yellow solid (13. 6 gm); mp ----°C;

IR (KBr) 2940, 2842, 2748, 1690, 1602, 1578, 1523, 1509, 1432, 1345, 1285, 1117, 1017, 815, 737 cm^{-1}.

^1H nmr (300 MHz, $CDCl_3$) δ 3.91 (s, 3 H), 6.9 (d, 1 H, , $J = 9.0$ Hz), 7.11 (d, 1 H, $J = 9.0$ Hz), 7.2 (t, 1H, $J = 7.8$ Hz), 7.48 (t, 1 H, $J = 7.8$ Hz), 7.51 (s, 1H), 7.71(dd, 1 H, $J = 7.8$ Hz, 1.8 Hz), 7.95 (d, 1H, $J = 7.8$ Hz,), 9.82 (s, 1 H).

Step 2: 3-(2-nitrophenoxy)-4-methoxyphenyl carboxylic acid; To a solution of 3-(2-nitrophenoxy)-4-methoxy benzaldehyde (10 gm, 0.036 mol) (from step 1) in acetone-

water mixture in 4: 1 ratio (75 mL) was added sulfamic acid (5.32 gm, 0.054 mol) while stirring at 0°C. A solution of 80% sodium chlorite (3.4 gm, 0.045 mol) in water (15.0mL) was added drop wise to the above reaction mixture over a period of 10 min. and was allowed to stir at 0°C for additional 30 min. The precipitate obtained was filtered, washed with water and air dried to give 12 gm of the product as white solid. mp ----°C;

IR (KBr)---- cm^{-1}.

^1H nmr (300 MHz, $CDCl_3$) δ 3.8 (s, 3 H), 6.9 (d, 1 H, J = 9.0 Hz), 7.28 (t, 1 H, J = 9.0 Hz), 7.30 (d, 1H, J = 9.0 Hz), 7.56 (s, 1 H), 7.6 (t, 1 H, J = 7.2 Hz), 7.85 (d, 1H, J = 8.4 Hz,), 8.02 (d, 1H, J = 8.4 Hz).

Step 3: 3-(2-aminophenoxy)-4-methoxyphenyl carboxylic acid; To a suspension of 3-(2-nitrophenoxy)-4-methoxyphenyl carboxylic acid (10 gm) (from step 2) in dichloromethane (500 ml) was added 5% Pd/C (10 % w/w) and hydrogenated at 40 psi for 3 h under hydrogen atmosphere. The catalyst was filtered over celite. The celite bed was washed with methanol. The combined filterate was concentrated in vaccuo to yield ththe desired product as pale yellow solid (8.5 gm). mp ----°C

IR (KBr) 3450, 3368, 2925, 1683, 1601. 1578, 1501, 1438, 1307, 1276, 1217, 1017, 788, 761 cm^{-1}.

^1H nmr (300 MHz, $CDCl_3$) δ 3.93 (s, 3 H), 6.63-6.68 (brm, 1H), 6.75 (m, 3 H), 6.91-7.0 (brm, 3H), 7.53 (s, 1 H), 7.80 (d, 1 H, J = 8.4 Hz).

Step 4 : 4-methoxy dibenzo[b,d]furan-1-carboxylic acid ; A suspension of 3-(2-aminophenoxy)-4-methoxyphenyl carboxylic acid (2 gm, 0.0077 mol) (from step 3) in a mixture of concentrated hydrochloric acid: water (1: 1) (20 ml) is warmed to 45oC for 10 min. and cooled to -5oC. A solution of sodium nitrite (630 mg, 0.0092 mol) in water (5 ml) is added dropwise to the above suspension at -5oC. The reaction mixture was stirred for 30 min and a chilled solution of sodium fluoroborate (1.26 gm, 0.0115 mol) was added to theabove reaction mixture and stirred at -5oC for 30 min. The diazonium

fluoroborate salt obtained (2.3 gm) as a result was filtered and washed with 5% cold sodium fluoroborate solution and air dried. The dried diazonium fluoroborate salt was added to a stirred suspension of cuprous oxide (1.76 gm, 0.0077 mol) in 0.1 N sulfuric acid (600 ml) at 35°C and stirred for 10 min. The resulting precipitate (2.0 gm) was filtered , washed with water, air dried and chromatographed on silica gel column using 20 % ethyl acetate in chloroform to give the desired product as a white solid (200 mg). mp :--°C

IR (KBr) 2925, 2853, 1688, 1607, 1512, 1490, 1437, 1277, 1221, 1023, cm^{-1}.

^1H nmr (300 MHz, DMSO) δ 4.05 (s, 3 H), 7.26 (d, 1 H, J = 8.7 Hz), 7.40 (t, 1 H, J = 7.2 Hz), 7.50 (t, 1H, J = 7.2 Hz), 7.74 (d, 1H, J = 8.1 Hz), 8.01 (d, 1H, J = 8.4 Hz), (8.85 (d, 1H, J = 7.8 Hz).

Step 5a : N-(3, 5-dichloropyrid-4-yl)-4-methoxy dibenzo[b,d]furan-1-carboxylic acid chloride

A suspension of 4-methoxy dibenzo[b,d]furan-1-carboxylic acid (100mg, 0.00413 mol) (from step 4) in a mixture of benzene (2 ml) and freshly distilled thionyl chloride (2 ml) was heated to reflux temperature for 1.5 h. The excess thionyl chloride was removed under vacuum to get the corresponding acid chloride which was subjected the next reaction as such.

Step 5b: N-(3, 5-dichloropyrid-4-yl)-4-methoxy dibenzo[b,d]furan-1-carboxamide

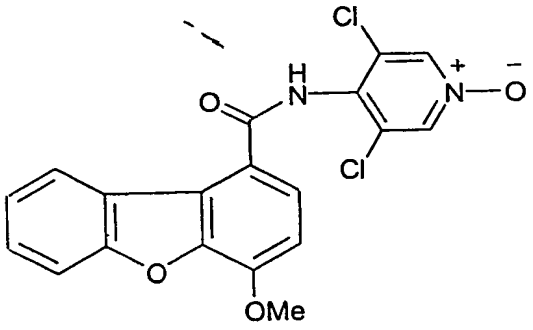
To a pre-washed suspension of sodium hydride (9.0 mg, 1.5 equiv., 61 mmol, 60% oil dispersion) in DMF (2 ml) was added drop wise a solution of 4-amino-3,5-dichloropyridine (68 mg, 41 mmol) in DMF (2 ml) at –10°C. A pre-cooled solution of above acid chloride (from step 5a) in THF (2 ml) was added, all at once, to the reaction mixture and the contents were stirred at –10°C for 30 min. The reaction was quenched with brine, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, 5 %HCl, 5% sodium bicarbonate and brine solution. Evaporation of solvent and washing of the resulting crude solid with methanol provided N-(3, 5-dichloropyrid-4-yl)-4-methoxy dibenzo[b,d]furan-1-carboxamide as a white solid (15 mg); mp: 302 °C.

IR (KBr) 3171, 2974, 1654, 1607, 1491, 1450, 1293, 1202, 1098, 101[illegible]756 cm^{-1}.

^1H nmr (300 MHz, DMSO) δ 4.07 (s, 3 H), 7.32 (d, 1 H, J = 8.4 Hz), 7.34 (t, 1 H, J = 8.4 Hz), 7.52 (t, 1H, J = 8.1Hz), 7.74 (d, 1H, J = 8.1 Hz), 7.89 (d, 1H, J = 8.4 Hz), 8.41 (d, 1H, J = 8.1 Hz), 8.77 (s, 2H), 10.8 (s, 1H).

Example 2

N-(3, 5-dichloropyrid-4-yl)-4-methoxy dibenzo[b,d]furan-1-carboxamide-N-oxide



Step 1: 3-(2-nitrophenoxy)-4-methoxy benzaldehyde ; To a stirred suspension of potassium fluoride (5.71 gm, 0.0985 mol) in dry DMSO (20 ml) was added a solution of isovanillin (10.0 gm, 0.0657 mol) in DMSO (20 ml). The reaction contents were heated at 140°C for 10 min. A solution of 2-fluoronitrobenzene (9.27 gm, 0.0657 mol) in DMSO (10 ml) was added to the above suspension and the reaction mixture was stirred at 140°C for 3.5 h. The reaction mixture was cooled to room temperature and the contents were poured into water (200 ml) and extracted with ethyl acetate (100 ml x 3). The organic extracts were combined and washed with 1N sodium hydroxide (50 ml x 2), water and brine and dried over anhydrous sodium sulfate. The dried organic layer was concentrated in vaccuo to obtain the product as a pale yellow solid (13. 6 gm); mp ----°C;

IR (KBr) 2940, 2842, 2748, 1690, 1602, 1578, 1523, 1509, 1432, 1345, 1285, 1117, 1017, 815. 737 cm^{-1}.

^1H nmr (300 MHz, $CDCl_3$) δ 3.91 (s. 3 H), 6.9 (d, 1 H, , J = 9.0 Hz), 7.11 (d, 1 H, J = 9.0 Hz), 7.2 (t, 1H, J = 7.8 Hz), 7.48 (t, 1 H, J = 7.8 Hz), 7.51 (s, 1H), 7.71(dd, 1 H, J = 7.8 Hz, 1.8 Hz), 7.95 (d, 1H, J = 7.8 Hz,), 9.82 (s, 1 H).

Step 2: 3-(2-nitrophenoxy)-4-methoxyphenyl carboxylic acid; To a solution of 3-(2-nitrophenoxy)-4-methoxy benzaldehyde (10 gm, 0.036 mol) (from step 1) in acetone-water mixture in 4: 1 ratio (75 mL) was added sulfamic acid (5.32 gm, 0.054 mol) while stirring at 0°C. A solution of 80% sodium chlorite (3.4 gm, 0.045 mol) in water (15.0mL) was added drop wise to the above reaction mixture over a period of 10 min. and was allowed to stir at 0°C for additional 30 min. The precipitate obtained was filtered, washed with water and air dried to give 12 gm of the product as white solid. mp ----°C;

IR (KBr)---- cm^{-1}.

^1H nmr (300 MHz, $CDCl_3$) δ 3.8 (s, 3 H), 6.9 (d, 1 H, J = 9.0 Hz), 7.28 (t, 1 H, J = 9.0 Hz), 7.30 (d, 1H, J = 9.0 Hz), 7.56 (s, 1 H), 7.6 (t, 1 H, J = 7.2 Hz), 7.85 (d, 1H, J = 8.4 Hz,), 8.02 (d, 1H, J = 8.4 Hz).

Step 3: 3-(2-aminophenoxy)-4-methoxyphenyl carboxylic acid; To a suspension of 3-(2-nitrophenoxy)-4-methoxyphenyl carboxylic acid (10 gm) (from step 2) in dichloromethane (500 ml) was added 5% Pd/C (10 % w/w) and hydrogenated at 40 psi for 3 h under hydrogen atmosphere. The catalyst was filtered over celite. The celite bed was washed with methanol. The combined filterate was concentrated in vaccuo to yield ththe desired product as pale yellow solid (8.5 gm). mp ----°C

IR (KBr) 3450, 3368, 2925, 1683, 1601, 1578, 1501, 1438, 1307, 1276, 1217, 1017, 788, 761 cm^{-1}.

^1H nmr (300 MHz, $CDCl_3$) δ 3.93 (s, 3 H), 6.63-6.68 (brm, 1 H), 6.75 (m, 3 H), 6.91-7.0 (brm, 3H), 7.53 (s, 1 H), 7.80 (d, 1 H, J = 8.4 Hz).

Step 4 : 4-methoxy dibenzo[b,d]furan-1-carboxylic acid ; A suspension of 3-(2-aminophenoxy)-4-methoxyphenyl carboxylic acid (2 gm, 0.0077 mol) (from step 3) in a mixture of concentrated hydrochloric acid: water (1: 1) (20 ml) is warmed to 45oC for 10 min. and cooled to -5oC. A solution of sodium nitrite (630 mg, 0.0092 mol) in water (5 ml) is added dropwise to the above suspension at -5oC. The reaction mixture was stirred for 30 min and a chilled solution of sodium fluoroborate (1.26 gm, 0.0115 mol) was added to theabove reaction mixture and stirred at -5oC for 30 min. The diazonium

fluoroborate salt obtained (2.5 gm) as a result was filtered and washed with 5° cold sodium fluoroborate solution and air dried. The dried diazonium fluoroborate salt was added to a stirred suspension of cuprous oxide (1.76 gm, 0.0077 mol) in 0.1 N sulfuric acid (600 ml) at 35°C and stirred for 10 min. The resulting precipitate (2.0 gm) was filtered , washed with water, air dried and chromatographed on silica gel column using 20 % ethyl acetate in chloroform to give the desired product as a white solid (200 mg). mp 270°C (dec.)

IR (KBr) 2925, 2853, 1688, 1607, 1512, 1490, 1437, 1277, 1221, 1023, cm^{-1}

^1H nmr (300 MHz, DMSO) δ 4.05 (s, 3 H), 7.26 (d, 1 H, J = 8.7 Hz), 7.40 (t, 1 H, J = 7.2 Hz), 7.50 (t, 1H, J = 7.2 Hz), 7.74 (d, 1H, J = 8.1 Hz), 8.01 (d, 1H, J = 8.4 Hz), (8.85 (d, 1H, J = 7.8 Hz).

Step 5a : N-(3, 5-dichloropyrid-4-yl)-4-methoxy dibenzo[b,d]furan-1-carboxylic acid chloride

A suspension of 4-methoxy dibenzo[b,d]furan-1-carboxylic acid (100mg, 0.00413 mol) (from step 4) in a mixture of benzene (2 ml) and freshly distilled thionyl chloride (2 ml) was heated to reflux temperature for 1.5 h. The excess thionyl chloride was removed under vacuum to get the corresponding acid chloride which was subjected the next reaction as such.

Step 5b: N-(3, 5-dichloropyrid-4-yl)-4-methoxy dibenzo[b,d]furan-1-carboxamide

To a pre-washed suspension of sodium hydride (9.0 mg, 1.5 equiv., 61 mmol. 60% oil dispersion) in DMF (2 ml) was added drop wise a solution of 4-amino-3,5-dichloropyridine (68 mg. 41 mmol) in DMF (2 ml) at –10°C. A pre-cooled solution of above acid chloride (from step 5a) in THF (2 ml) was added, all at once, to the reaction mixture and the contents were stirred at –10°C for 30 min. The reaction was quenched with brine, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, 5 %HCl, 5% sodium bicarbonate and brine solution. Evaporation of solvent and washing of the resulting crude solid with methanol provided N-(3, 5-dichloropyrid-4-yl)-4-methoxy dibenzo[b,d]furan-1-carboxamide as a white solid (15 mg); mp: 302 °C.

IR (KBr) 3171, 2974, 1654, 1607, 1491, 1450, 1293, 1202, 1098, 1011, 756 cm^{-1}.

^1H nmr (300 MHz, DMSO) δ 4.07 (s, 3 H), 7.32 (d, 1 H, J = 8.4 Hz), 7.34 (t, 1 H, J = 8.4 Hz), 7.52 (t, 1H, J = 8.1Hz), 7.74 (d, 1H, J = 8.1 Hz), 7.89 (d, 1H, J = 8.4 Hz), 8.41 (d, 1H, J = 8.1 Hz), 8.77 (s, 2H), 10.8 (s, 1H).

Step 6: N-(3, 5-dichloropyrid-4-yl)-4-methoxy dibenzo[b,d]furan-1-carboxamide-N-oxide

A suspension of N-(3,5-dichloropyrid-4-yl)-4-methoxy dibenzo[b,d]furan-1-carboxamide (200 mg, 0.518 mmol) and m-chloroperbenzoic acid (50-55%) (880 mg, 2.5 mmol) in chloroform (10 ml) was refluxed for 2 h. The reaction was cooled and washed with saturated sodium bicarbonate and water. The organic solvent was distilled of in vaccuo and the residue was purified by column choromatography using 20 % acetone-chloroform as the eluent to give 150 mg of N-(3, 5-dichloropyrid-4-yl)-4-methoxy dibenzo[b,d]furan-1-carboxamide-N-oxide as white solid; mp: 265-270°C.
IR (KBr) 3214, 3060, 3007, 2931, 1655, 1474, 1454, 1282, 1245, 1099, 1011, 751 cm^{-1}.

^1H nmr (300 MHz, DMSO) δ 4.07 (s, 3 H), 7.33 (d, 1 H, J = 8.4 Hz), 7.35 (t, 1 H, J = 8.4 Hz), 7.55 (t, 1H, J = 8.1Hz), 7.74 (d, 1H, J = 8.1 Hz), 7.88 (d, 1H, J = 8.4 Hz), 8.41 (d, 1H, J = 8.1 Hz), 8.76 (s, 2H), 10.64 (s, 1H).

Dated this Twenty third (23rd) day of October 2002

(CHERYL PINTO)
Director
Glenmark Pharmaceuticals Limited

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☑ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☑ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.